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Pharmacogenomics in diabetes mellitus – insights into drug action and drug discovery

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Abstract | Genomic studies have greatly advanced our understanding of the multifactorial aetiology of type 2 diabetes mellitus (T2DM) as well as the multiple monogenic diabetes subtypes. In this Review, we discuss the existing pharmacogenetic evidence in both monogenic diabetes and T2DM, highlight the mechanistic insights from the study of side effects to antidiabetic drugs as well as their efficacy. The identification of extreme sulfonylurea sensitivity in patients with diabetes mellitus caused by heterozygous mutations in *HNF1A* represents a clear example of how pharmacogenetics can impact on patient care. However pharmacogenomic studies of response to antidiabetic drugs in T2DM has yet to translate into clinical practice, although some moderate genetic effects have now been described that merit follow up in genotype selected trials. We also discuss how future pharmacogenomic findings could provide insights into treatment response in diabetes that, complementary to other areas of human genetics, facilitates drug discovery and drug development for T2DM.

Introduction

In the past decade, genome-wide association studies (GWAS) and high-throughput sequencing, propelled by the fast development in affordable genomic technologies, have greatly advanced our understanding of the genetic aetiology of many common diseases[1]. Pharmacogenomic studies applying these genome-wide approaches to investigate drug response have also yielded important results[2, 3]. In this Review, and in this context, we discuss the genomic evidence that has strengthened our understanding of the multifactorial aetiology of type 2 diabetes mellitus (T2DM) and discuss the emerging evidence that a complex genetic architecture might underline the variation in response to antidiabetic drugs.

Genetic evidence in disease genomics is increasingly being used for target validation in drug discovery. We anticipate how robust pharmacogenomic evidence could provide more valuable information to predict both on-target and off-target effects in drug discovery and development.

The multifactorial aetiology of T2DM

T2DM is a complex metabolic disease characterized by hyperglycaemia resulting from functional impairment in insulin secretion, insulin action or both[4]. Both insulin resistance and secretory deficiency arise through the interplay of genetic and environmental risk factors[5]. GWAS, which have interrogated all the common genetic variants (minor allele frequency greater than 5%), have identified >120 T2DM risk loci[6, 7]. High-throughput sequencing studies, which could theoretically examine all the variants in the genome or at least the section that encodes proteins, have also enabled the discovery of rare variants (minor allele frequency <5%) at GWAS identified loci and novel loci for T2DM[8, 9]. Together these common variants with small to moderate effects and rare variants with relatively large impacts could account for ~15% of the total risk of developing T2DM and confirm its nature as a multisystem disorder[6, 10].

Glycaemic control is a key focus in the management of T2DM, and is associated with both microvascular and macrovascular benefits[11-13]. The treatment of T2DM has evolved with our understanding of the pathophysiology of this complex disease[5]. A wide range of drug treatment, characterized by different mechanism of action, is available to achieve glycaemic control in patients with T2DM (Figure 1)[14]. Apart from insulin replacement, traditional oral agents include the secretagogues that stimulate the pancreas to release insulin and the sensitizers that enhance the efficacy of insulin action[14]. New agents include the dipeptidylpeptidase-4 (DPP4) inhibitors, also known as the gliptins, that enhance the so-called 'incretin effect' and promote glucose-stimulated insulin secretion[15]; as well as the sodium-glucose cotransporter-2 (SGLT-2) inhibitors that reduce hyperglycaemia by increasing glucose elimination via the urine[16]. Although these drugs are all effective at lowering glucose in patients with T2DM, glycaemic control often fails even after a combination of the available treatment options due to the progressive nature of the disease.

Diabetes drug response can be considered at many levels, as outlined in Table 1, including the physiological response to the drug, or the long term effect of the drug in terms of microvascular or macrovascular risk reduction. In this Review, when considering drug response, we focus primarily on the glycaemic effect of drugs as this outcome has been the most studied.

Monogenic diabetes mellitus

With the increasing awareness that T2DM is highly heterogeneous, and as we understand more about the aetiology of the disease, we can begin to subdivide 'T2DM' into distinct aetiological subtypes. This development can be seen with the increasing identification of monogenic forms of the disease, which until the past 10-15 years were misclassified as type 1 diabetes mellitus or T2DM. Understanding these aetiological subtypes has resulted in some of the earliest studies that provided the most clinically robust examples of pharmacogenetics to date. For example, patients with Maturity Onset Diabetes of the Young owing to mutations in *HNF1A* (which accounts for ~3% of all diabetes mellitus cases diagnosed under the age of 30 years) are extremely sensitive to sulfonylurea treatment, and can successfully transition off insulin treatment[17]. Similarly patients with neonatal diabetes due to *KCNJ11* or *ABCC8* mutations who have insulin dependent diabetes mellitus from soon after birth have been shown to respond to high dose sulfonylureas and to be able to transition off insulin onto oral sulfonylurea treatment[18]. These examples highlight how increasing awareness of aetiological subtypes of diabetes will enable a precise approach to treatment of diabetes mellitus and is an area of great interest. However, for the remainder of this review, we will focus on polygenic influences on drug response in T2DM.

Pharmacogenomics and genetic architecture

Pharmacogenetics aims to seek the genetic explanation of why individuals respond differently to drugs, both in terms of therapeutic efficacy as well as adverse drug reactions (ADR)[19]. Prior to the emergence of genome wide genotyping arrays, pharmacogenetic studies focused on candidate genes with known links to drug distribution, metabolism or response pathways[19]. With the development of cost-effective genomic technologies, genome-wide genotyping and sequencing has transformed this traditional pharmacogenetic approach into a more global pharmacogenomic approach that can systematically interrogate millions of genetic polymorphisms across the genome[20, 21]. Most published genome-wide studies of drug response are GWAS, and only a few such studies reported sequencing-based investigations. One example of a sequencing-based study is the use of publicly available whole-genome sequence data on 482 samples to profile 231 pharmacogenetic genes[22]. In the same study, the authors also performed whole genome sequencing on 7 family members to try to explain the genetic basis of their variable response to anticoagulation treatment. The two terms pharmacogenetics and pharmacogenomics are often used interchangeably, but in this Review we use pharmacogenomics to refer to studies using genome-wide approaches.

Biomarker discovery for precision medicine remains the long-term goal of pharmacogenomic studies. However, an often under-appreciated benefit of such studies is that they can advance our understanding of the biological mechanism of drug action in humans by identifying variants in genes not previously thought to be associated with drug response. These genes might never have been included in traditional candidate gene approaches[3].

A fundamental issue underlying the validity and feasibility of pharmacogenomic studies is the genetic architecture of drug response[23]. In this context 'genetic architecture' refers to the number of response variants; the frequency spectrum of these response variants; the effect size spectrum of the variants; the physical distribution of the variants in the genome; and the amount of variation in drug response explained by these genetic variants (known as heritability). Whilst heritability determines the validity of pharmacogenomic studies, the other aspects of genetic architecture dictate the feasibility and design of pharmacogenomic studies.

Adopting traditional twin and family study designs to estimate the heritability of drug treatment outcomes has been largely impractical, because family members may not develop the same disease or be treated with same drug. With the availability of GWAS data, new 'chip-based' approaches have been developed to estimate heritability from population-based samples[24]. However, data from at least a few thousand individuals are required to achieve an accurate estimate of heritability by these methods[25]. Such methods, therefore, can be applied to estimate the heritability of treatment efficacy for commonly used drugs, but not the less frequent ADRs.

In a study of GWAS data from 2,085 patients with T2DM, heritability of glycaemic response to metformin was estimated to be up to 34% (p=0.02)[23]. Furthermore, this investigation also found that the heritability is likely to be the result of many common response variants with small to moderate effect sizes scattered across the genome[23]. These results suggest that the genetic architecture of metformin efficacy is similar to that of T2DM and other complex traits. This similarity between the genetic architectures of T2DM and the treatment efficacy of metformin is likely to be rooted in the multifactorial aetiology of the disease. Variants in different genes or pathways might affect metformin treatment efficacy in patients whose pathophysiology is heterogeneous (for example, those individuals who are predominantly insulin resistant or those whose insulin secretion is deficient). Similar to metformin, other antidiabetic agents are also used to treat a combination of patients with heterogeneous pathophysiology. Therefore we anticipate that the genetic architecture of treatment efficacy for other antidiabetic agents to be similar to that of metformin response.

To appreciate the scale of the heritability estimate of 34% for glycaemic response to metformin, it is necessary to put it into the context of other complex traits. In a 2015 study again using a population-based method, the heritability estimate for BMI was 27%(S.E.=2.5%) [26], which is considerably lower than the heritability estimates of 40%~60% derived from traditional twin and family studies[27]. The discrepancy observed between the two methods could be explained by the facts that heritability is underestimated by the 'chip-based' method due to imperfect tagging and it is often overestimated by the traditional twin studies due to common environment confounding[28]. Therefore the actual heritability of glycaemic response to metformin could be even higher than what has been estimated from GWAS data. In addition, chip-based heritability estimates also suffer underestimation due to the incomplete coverage of contribution from rare variants, whereas traditional twin and family studies are unbiased in this regard[24]. Finally, the diversity of the microbiota residing in the gut might also contribute to the variable response to metformin. For example, metformin-associated change in gut microbiome accounts for a considerable proportion of the difference in taxonomic composition between patients with T2DM and non-diabetic controls[29]. Examining the diversity of this gut microbiome might, therefore, enable the identification of novel targets for the prevention or management of T2DM as the microbiota genome is easier to modify with prebiotics or probiotics compared to the host genome[30].

Notably, twin and family studies have been used to estimate the heritability of physiological response to antidiabetic agents in participants without T2DM. For example, in a twin-family study of 100 healthy twins and 25 siblings, the heritability of GLP-1 stimulated insulin secretion during hyperglycaemia to be 53%[31]. In another family study, the heritability of tolbutamide stimulated insulin secretion (Acute Insulin Response$_{tolbutamide}$) in 284 healthy family members of patients with T2DM was estimated to be 69%[32]. The results of these twin and family studies that include non-diabetic individuals have demonstrated that a large component of the variation in physiological measures in response to antidiabetic drugs is contributed by genetic variants. However, to what extent such high heritability estimates are comparable to that of glycaemic response estimated from population-based studies of patients with T2DM is unclear. Two reasons might account for different heritability estimates between the two study designs. Firstly, twin and family studies are often performed in controlled settings, which have less environmental variance than real world patient populations. Consequently, the same genetic effect sizes could lead to higher heritability estimates. Secondly, the pharmacodynamics in patients with T2DM might differ from that in healthy individuals as the mechanism of glycaemic homeostasis could vary by physiological states in which different functional pathways are involved[33].

Most of the robust findings in pharmacogenomic studies to date are related to severe ADRs[2]. The variants associated with these rare ADRs often confer a large risk. For example carrying the HLA-B*57:01 allele causes an 80 fold (p=9.0x10^{-9}) increased risk of flucloxacillin induced liver injury compared to non-carriers of this allele[34]. Encouraged by findings like this, it has been proposed that many of the drug-response variants should have considerable, clinically significant impact on treatment outcome[35, 36]. This proposal is supported by the hypothesis that drug response variants lack the evolutionary constraint that has filtered out large disease risk variants via natural selection[35]. However, two explanations exist as to why large impact pharmacogenomics variants are unusual, especially for variants affecting treatment efficacy. Firstly, pharmaceutical interventions often achieve clinical impact via complex metabolic networks, which rely on redundant pathways and synergistic effects to maintain their robustness when confronted with external stimuli[37]. Partial or complete impairment of one node in the network is, therefore, more likely to have marginal impact on the treatment efficacy than a complete shutdown on all the relevant pathways. Secondly, the established spectrum of large impact ADR variants might also reflect a publication bias, which accumulated the so called 'low hanging fruit' that have been identified by pharmacogenomic studies often using fewer than 1000 cases[3, 38]. Although the genetic architecture of rare ADRs might be akin to those of polygenic diseases in which large impact variants dominate[3], we anticipate the genetic architecture of treatment efficacy and mild ADRs would both encompass a spectrum of rare-to-common variants with moderate effect sizes. This notion is in line with the fact that rare variants with moderate impact have been successfully identified for common diseases such as T2DM by sequencing and imputation-based rare variant association studies of over one hundred thousand samples[9]. Assembling large samples would, therefore, enable the identification of more drug response variants by future pharmacogenomic studies.

Pharmacogenomics of T2DM drugs

Owing to the considerable variability in response to existing drugs to treat diabetes mellitus, a large number of pharmacogenetic studies have been published, but only one pharmacogenomic GWAS study of metformin treatment efficacy reported[39]. These studies each focused on a single oral agent and have been the subject of many previous reviews [40-42]. No report exists on the pharmacogenetics of drug-drug interaction, despite a large number of patients requiring multiple agents to combat diabetes progression and maintain glycaemic control. In this section we summarize the replicated findings in studies of treatment efficacy and place more emphasis on the investigation of adverse effects (Table 2).

Treatment efficacy

Very few robust pharmacogenetic findings related to treatment efficacy of diabetes mellitus drugs have been reported. Previous candidate gene studies largely focused on drug transporters or metabolizing enzyme variants that have been implicated in the pharmacokinetics of drug exposure[41]. Variation in metformin pharmacokinetics is mainly the result of variants in transporters *SLC22A1* (encoding OCT1) and *SLC47A1* (encoding MATE1)[43, 44]. However, the most investigated reduced-function OCT1 variants with low transporter activity showed no consistent impact on glycaemic control in patients[45-48]. Sulfonylureas are mainly metabolized by Cytochrome P450 2C9 which is encoded by *CYP2C9*. Individuals with the loss-of-function variants in *CYP2C9* have higher drug exposure, and this in turn does lead to consistent observations of greater glycaemic response than those carrying the wild-type alleles[49-51].

Studies of potential pharmacodynamic variants, which might affect how antidiabetic agents alter glucose levels, have largely focused on the genes involved in glucose metabolism and the risk of developing T2DM. One replicated finding is seen for *TCF7L2* and sulfonylurea response, where the allele associated with reduced β-cell function and, therefore, increased risk of T2DM is also associated with reduced efficacy of sulfonylureas[52-54]. The K allele of the E23K variant in *KCNJ11*, which encodes the known targets of sulfonylureas, also had association with greater glycaemic response in multiple studies[55-57]. These observations of E23K carriers were consistent with the evidence that neonates with monogenic diabetes who have causal variants in *KCNJ11* could be effectively treated with sulfonylureas[18]. Another replicated finding is the association between *PPARG* Pro12Ala variant and response to Thiazolidinediones (commonly known as TZDs). A few studies each using less than 200 participants consistently reported the T2DM risk Pro allele is associated with poor glycaemic response [58-60]. For the newer agents such as gliptins and SGLT2 inhibitors, pharmacogenetic studies of treatment efficacy have been sparse with only one relatively large study reporting the association and replication between **rs7202877** near CTRB1/2 and response to gliptins[61].

The only GWAS of any antidiabetic agent published to date identified a variant rs11212617 near the *ATM* locus being associated with glycaemic response to metformin[39]. Independent replications were later reported in multiple cohorts of different ancestries, strengthening the evidence that the variant is the most established drug response variant for antidiabetic drug[62, 63]. Given the moderate impact on glycaemic response to metformin, this variant is not a useful biomarker that can substantially increase our ability to accurately predict the treatment outcome in individual patients. However, as this variant has no functional link to any known metformin mode-of-action, it demonstrates that such a pharmacogenomic

discovery could reveal novel mechanisms of action of an antidiabetic drug, which might in turn identify further pathways to target with new therapeutic agents. The finding that variants near *ATM* are associated with metformin response has prompted further study of the genes at this locus in relation to glucose metabolism and metformin response. For example, in a small study of patients with ataxia telangiectasia who have recessive loss of function mutations in *ATM*, the investigators identified an impaired glucose tolerance and insulin resistance supporting a potential role for *ATM* in glucose metabolism and metformin response[64].

ADRs

Pharmacogenetic studies have also been performed to help in the understanding of ADRs associated with antidiabetic drugs. Key ADRs studied include sulfonylurea-induced hypoglycaemia, TZD-associated oedema, hepatotoxicity and heart failure, and metformin associated gastrointestinal (GI) disturbance[65-69]. To date, no studies have been published on the pharmacogenomics of the potentially fatal but rare ADRs of metformin-associated lactic acidosis[70]. Thus far, the investigators in all the published pharmacogenetic studies have adopted a candidate gene approach. For sulfonylurea-induced hypoglycaemia, a number of small studies using no more than 108 patients have been conducted and they consistently showed that the loss-of-function *CYP2C9* variants, which are associated with increased drug exposure[66], are also associated with a higher risk of hypoglycaemia[65], which is consistent with the efficacy studies showing these variants are associated with greater glucose reduction than wild-type alleles[45]. For TZDs, the results have indicated that variants in *GSTT1* and *CYP2C19* were associated with troglitazone-induced hepatotoxicity[68, 71]; whilst variants in *NFATC2* are associated with the rate of rosiglitazone-induced oedema[67]. Although some safety concerns have been raised against the newer agents, such as genital and urinary tract infections associated with SGLT2 inhibitors and the pancreatitis and liver dysfunction associated with gliptins[70], to our knowledge, no pharmacogenetic reports on these ADRs exist.

Metformin causes gastrointestinal disturbance in as many as 20-40% of patients with 5-10% of patients not being able to tolerate this drug[70]. The biological mechanism for gastrointestinal intolerance to metformin remains poorly understood. Based on the hypothesis that individuals who are intolerant of metformin are exposed to higher concentrations of the drug in the gastrointestinal tract, investigators have explored variants in transporter genes such as OCT1[72]. In a large study of 2,166 patients, both reduced-function variants in OCT1 and co-medication of certain OCT1 inhibitors (that is, verapamil, proton pump inhibitors, citalopram, codeine and doxazosin) significantly increased the risk of metformin induced gastrointestinal side effect[69]. The combination of carrying the genetic

variants and taking co-medications could result in a four-fold (p<0.001) increased risk of gastrointestinal side effect[69]. Therefore this large impact on metformin induced gastrointestinal side effects by these OCT1 variants have the potential to be translated into clinical practice by prescreening the patients on OCT1 genotype and co-medication of OCT1 inhibitors. Moreover, this study highlighted two key factors for successful pharmacogenomics of antidiabetic drugs: large sample sizes are required for adequate statistical power; and the need to consider co-prescribed medication that potentially interacts with these agents. This result has since been replicated in an independent study which showed the same genetic variants were associated with increased risk (OR=2.3; p=0.02) of less severe metformin intolerance[73].

Genetics and drug target validation

A major challenge in the modern pharmaceutical industry is that fewer than 15% of drugs entering the development pipeline make it to market[74], a vastly expensive, inefficient and wasteful process. Toxicity and lack of efficacy both contribute to the high failure rate of new drugs development, which reflects the ineffectiveness of conventional target validation methods used in preclinical studies. Moreover, the model systems used in the preclinical studies often fail to represent the real biological system working in humans.

Genetic variants that arise as a result of historical mutation and recombination events can be viewed as naturally occurring experiments that perturb human gene function. These naturally occurring mutations are an opportunity to see the impact of perturbing a gene (for example, by a potential novel drug) on disease risk and off-target effects without the need to develop and trial the drug. For example, in a large survey of 61,104 drugs across the various stages of development, those drug candidates that targeted proteins encoded by genes with robust human genetic evidence (GWAS evidence or link to Mendelian diseases in OMIM) are twice as likely to be therapeutically valid[75].

To address the question of how to harness the human genetic evidence to guide target validation in drug development, the 'therapeutic hypothesis' has been proposed[76]. Central to this approach is the concept of a genetic evidence based 'dose-response' curve. An example of translating such a hypothesis into a new drug is the development of the PCSK9 inhibitors to reduce levels of LDL cholesterol[77]. Rare 'gain-of-function' variants in *PSCK9* led to high levels of LDL cholesterol and increased the incidence of coronary heart disease risk[78]. Conversely, rare 'loss-of-function' variants resulted in lower LDL cholesterol levels and a reduced risk of coronary heart disease[79]. GWAS also identified common variants in other genes such as SORT1 and LDLR with mild impact on LDL cholesterol levels and risk of coronary heart disease[80, 81]. These experiments (which are essentially designed by nature)

have demonstrated that reducing levels of LDL cholesterol and the risk of coronary heart disease is possible by inhibiting the function of *PCSK9* without any observable adverse effects[77]. With further support by other mechanistic evidence derived from model systems, a new generation of LDL cholesterol lowering *PCSK9* inhibitors have been developed, tested and licensed for use[82].

Dozens of common and rare variants have been convincingly associated with glycaemic control and the risk of developing T2DM[10]. Representatives from both academia and pharmaceutical companies have now formed the Accelerating Medicines Partnership to enhance the translation of human genomic research outputs into the development of new drugs (https://www.nih.gov/research-training/accelerating-medicines-partnership-amp)[83]. As one of the three prioritized area, the Accelerating Medicines Partnership aims to establish an open-access portal for T2DM genetics research (http://www.type2diabetesgenetics.org), which will pool genomic and phenotyping data to facilitate novel data mining efforts[83]. One target of potential interest raised by the Accelerating Medicines Partnership is the zinc-transporter-encoding *SLC30A8.* The use of GWAS has established robust evidence that the common coding variant Arg325Trp is associated with the risk of T2DM[84]. The results of mechanistic studies in humans and mice have both indicated that the reduced zinc transporter activity allele is associated with an increased risk of T2DM[85, 86]However, in a sequencing based study of ~150,000 individuals**,** rare protein-truncating variants In *SLC30A8* protected the carriers from developing T2DM[9]. This conflicting genetic evidence does not provide a consistent dose-response curve based on the functional characterization of the variants[87]. Further mechanistic studies, especially those involving intensive phenotyping of individuals carrying rare extreme functional *SLC30A8* variants will be useful to validate whether inhibiting or enhancing the zinc transporter 8 function could be the therapeutic option for treating T2DM. The example provided by *SLC30A8* demonstrates that human genetic evidence is not always sufficient to validate a gene/protein as a drug target, especially in situations when uncertainty surrounds the exact mechanism of how target genes alter a phenotype of interest.

The discovery of sodium glucose transporter 2 (SGLT2) inhibitors to treat T2DM is another example of how genetic evidence can be used in assisting drug development (Figure 2). Early evidence indicated that phlorizin, a natural inhibitor of SGLT2 and isolated from the bark of apple trees, restored euglycaemia and insulin sensitivity in animal models of T2DM[88]. After the cloning of *SLC5A2* which encodes SGLT2, functional variants in SGLT2 have been linked to familial renal glycosuria (http://www.omim.org/entry/233100)[89]. Patients with familial renal glycosuria, who carry a spectrum of >50 mild heterozygote to severe homozygote SGLT2 loss-of-function variants, have different levels of glycosuria but apparently normal

renal functions, normal glucose concentrations and general health[90]. Here the genetic evidence not only validated the therapeutic potential of inhibiting SGLT2 but also provided critical evidence that selective inhibitors targeting the protein would result in no long-term ADRs. Consequently, several selective SGLT2 inhibitors have been successfully developed and licensed to treat T2DM[14]. Aside from their glucose lowering effect, these SGLT2 inhibitors have an average impact of 1.63kg (p<0.001) weight reduction benefit[16, 91], which is increasingly being considered as an important component in the management of T2DM[92].

Pharmacogenomics and drug discovery

Conventional pharmacogenetics, which is based on candidate genes has been used in all stages of the drug development pipeline, from target identification, to clinical trials and postmarket analysis of ADRs[35]. As pharmacogenetics moves to pharmacogenomics, this genome-wide hypothesis free approach could also have more applications in drug discovery and development[20].

The proposed 'therapeutic hypothesis' is based on the principle that human genetics is an experiment of nature, which shows what phenotypic outcomes the natural perturbations of gene functions can lead to in a human population[76]. Clearly human genetics has the advantage that the experimental system is in living humans as opposed to the cell or animal model systems used in preclinical studies. However, the ideal system for validating a therapeutic hypothesis would be a genetic study carried out in the exact context the new drug is developed for. Genetic evidence of disease risk could be useful in validating the targets for a preventive drug but less informative to predict the therapeutic potential for disease management. For example, let us consider using human genetic evidence to validate candidate drug targets to improve glycaemic control in patients with T2DM. The most available candidates would be those genes with established variants associated with the risk of developing T2DM or poor glycaemic control in the general population. However, it has been suggested that the mechanism regulating glycaemia can vary between different physiological states[33]. The variants affecting glycaemia in normal individuals and those associated with T2DM risk only partially overlap[33], suggesting perturbations of glycaemia are not always linked to the risk of T2DM. Similarly, the variants conferring risk to T2DM have little impact on the rate of disease progression[93], which suggests that the mechanism controlling glycaemia when T2DM has developed might be different from those involved in its development. Consequently, targeting the genes involved in regulation of glycaemia in healthy individuals or the risk of T2DM might not have the desired glycaemic impact on the management of T2DM, especially if their biological functions have been altered by the onset of the disease. In the context of disease management, pharmacogenomic studies of existing

antidiabetic drugs can identify genes involved in glycaemic control in patients with T2DM. Robust pharmacogenomic findings would, therefore, provide physiological state specific information for drug target validation in addition to other evidence of normal glycaemic control and risk of T2DM derived from human genetic studies.

Table 1 outlines the differences between pharmacogenomic studies of drugs to treat T2DM and genomics of other diabetes mellitus-related traits. Compared to the wealth of findings from other areas of human genetics, to date pharmacogenomics has yielded less robust results, in part owing to the challenge to assemble tens of thousands of samples that could provide adequate statistical power to detect variants with moderate effect. However, we anticipate future drug discovery and drug development to benefit more from the pharmacogenomic findings derived from larger samples that are increasingly available from biobanks linked to electronic health record data (e.g. the UKBiobank). Notably, longitudinal data from clinical trials or health record linkage do enable the study of outcomes other than simple measures of glycaemia. For example, given a sufficient sample size, using pharmacogenomics to assess cardiovascular endpoints of antidiabetic drugs might be possible. In addition, large samples would also enable pharmacogenomics to joint analyse multiple outcomes (for example both glycaemic benefit and weight benefit of metformin), which would help to identify variants associated with pleiotropic effects of antidiabetic drugs.

Avoiding ADRs or off-target effects is also an important consideration in drug development. The very existence of ADRs is an illustration of our incomplete understanding of the complex interactions between our biological system and any designed interventions[94]. The increased availability of genome-wide screening tools will enable the identification of more ADR variants at an early stage of drug development, which has a number of clear advantages. For example, if the ADR variants were identified before phase 3 clinical trials, recruitment by genotype trials could be performed to evaluate the efficacy and risk in stratified patient subgroups[35]. When a drug is approved for marketing, understanding the genetic basis of severe ADR could also help the continuous development of the drug by prescreening the genotype ahead of treatment[95].

A system biology view of drug response

One of the biggest challenges facing contemporary biological research is to understand the complex biological networks that function in a living system[96]. This complexity can be seen in T2DM, where the genes harbouring the established aetiological variants have an excess of interactions within a high-confidence interaction network[97]. The variants in this network affect the protein function, stability of protein or transcript, and expression of individual genes, which collectively perturb or rewire the network structure to alter the risk of T2DM[98, 99].

Interestingly, when considering a network of disease genes and genes encoding known drug targets, the distance between genes reported in GWAS and known drug targets are shorter than that between random gene-drug targets pairs[100]. This is predominantly driven by a three-fold enrichment of drug target genes among the first neighbours of the GWAS reported genes. More evidence of direct overlap between the drug target genes and disease risk genes was also presented in a gene set enrichment analysis[101]. In this study a set of 102 target genes for existing diabetes mellitus drugs (e.g. insulin, metformin and TZDs), as curated from the literature, showed significant enrichment of genetic association with T2DM susceptibility[101]. Such findings indicate that potential drug targets are enriched in a disease network, but might only be identified when considering the network as a whole, rather than individual disease genes.

When modelling a drug intervention in a functional network, it is important to consider how the drug alters the functional network at the levels of cell, tissue and disease state, which will ultimately determine the beneficial and harmful effects of the drug. So far our knowledge of biological networks has been largely limited to the generic, static models lacking such contextual information[102]. Research in system biology is beginning to offer more comprehensive cell lineage and tissue specific networks[103-105], which will enable the modelling of drug intervention in more specific contexts such as the cell type, tissue and the physiological state. Such analyses will provide insights into how drugs can achieve the desired therapeutic effect in target tissue or known site of action, but importantly highlight the potential undesirable off-target effects in other contexts. Moreover, adopting a system-wide approach might change the focus of drug development for complex diseases such as T2DM from targeting an individual protein or gene to system-wide attacks on multiple dynamic targets[106].

Conclusions

The availability of affordable high-throughput genomic technologies has expanded our knowledge about the multifactorial aetiology of T2DM. Studies adopting such genome-wide approaches to investigate the response of existing antidiabetic drugs have been limited, but have the potential to improve our understanding of the biological mechanisms underlying treatment efficacy and side effects. With the major investments in precision medicine in the US[107], the 100,000 genomes project in the UK[108], and the EU funded stratified medicine in diabetes mellitus initiative IMI-DIRECT[109] (Innovative Medicines Initiative: DIabetes REsearCh on patient straTification), more findings from adequately powered pharmacogenomic studies are expected to complement other human genetic discoveries to facilitate more efficient antidiabetic drug discovery programs.

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Key points

- The list of known variants affecting type 2 diabetes mellitus (T2DM) risk confirms that this disease has a multifactorial aetiology

- The concept of precision medicine has been exemplified in pharmacogenetic studies of monogenic diabetes

- The genetic architecture of mild adverse drug reactions and treatment efficacy for antidiabetic agents probably resembles that of T2DM and other complex traits

- Existing pharmacogenetic evidence of T2DM is limited; future pharmacogenomics studies utilizing large samples will help identify variants that reveal novel mechanism of drug action

- Genetic evidence-based 'dose-response' curves have been used in validating candidate drug targets

- Pharmacogenomic studies adopting a system biology approach are expected to provide context specific evidence for future T2DM drug development

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Competing interests statement

The authors declare no competing interests.

Contributions

All authors contributed to all aspects of the manuscript.

Figure 1 | Target organs and action mechanism of antidiabetic drugs. The mechanism for metformin action remains uncertain: metformin might target the liver to reduce gluconeogenesis and skeletal muscles to enhance peripheral glucose utilization[110] with a possible role in the gut to increase levels of GLP-1[111]. Sulfonylureas and meglitinides increase insulin secretion in the pancreas[112, 113]. Thiazolidinediones (TZDs) act as insulin sensitizers in the skeletal muscle, adipose tissue and the liver[114]. GLP-1 agonists target the pancreas to increase insulin secretion and reduce glucagon production, as well as act in the gut to reduce gastric emptying[115]. DPP-4 inhibitors increase the level of endogenous incretin levels by blocking the action of a catalytic enzyme DPP-4[115]. SGLT-2 inhibitors reduce renal glucose reabsorption[116]. Abbreviations: DDP4, dipeptidyl peptidase 4, GLP1RA, glucagon like peptide 1 receptor agonist, SGLT2I, sodium glucose transporter 2 inhibitor
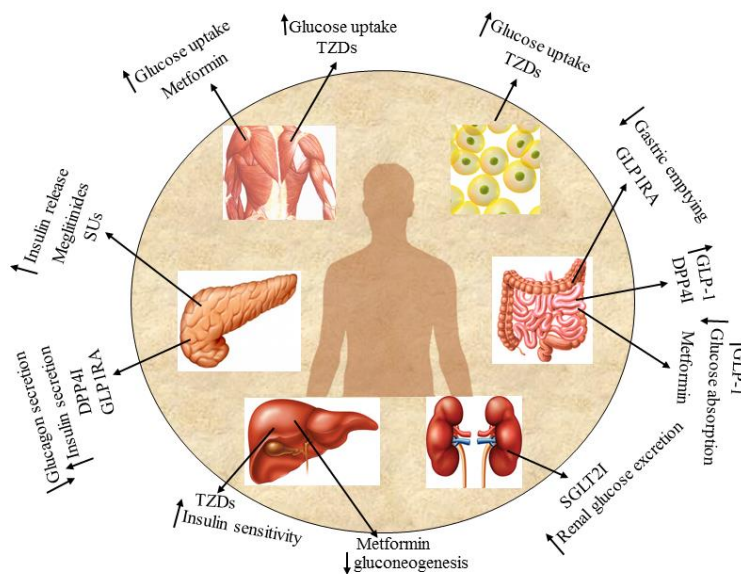
Figure 2 | Dose-response curve for the therapeutic hypothesis of selective SGLT2 inhibitors. The Y axis represent the range of glucose level, in which the high range represents the hyperglycaemic state seen in T2DM as compared to the normal range seen in healthy individuals or those patients with familial renal glycosuria. The X axis represents a spectrum of naturally occurring SGLT2 loss-of-function variants observed in patients with familial renal glycosuria. The variants were ordered from the mild heterozygotes to the severe homozygotes as defined by the resulting severity of glycosuria. For on-target adverse reactions, the benign glucosuria and apparently normal health seen in these patients also supports the safety profile of selectively inhibiting SGLT2 function in a wide dose window. Abbreviation: SGLT2, sodium glucose transporter 2.
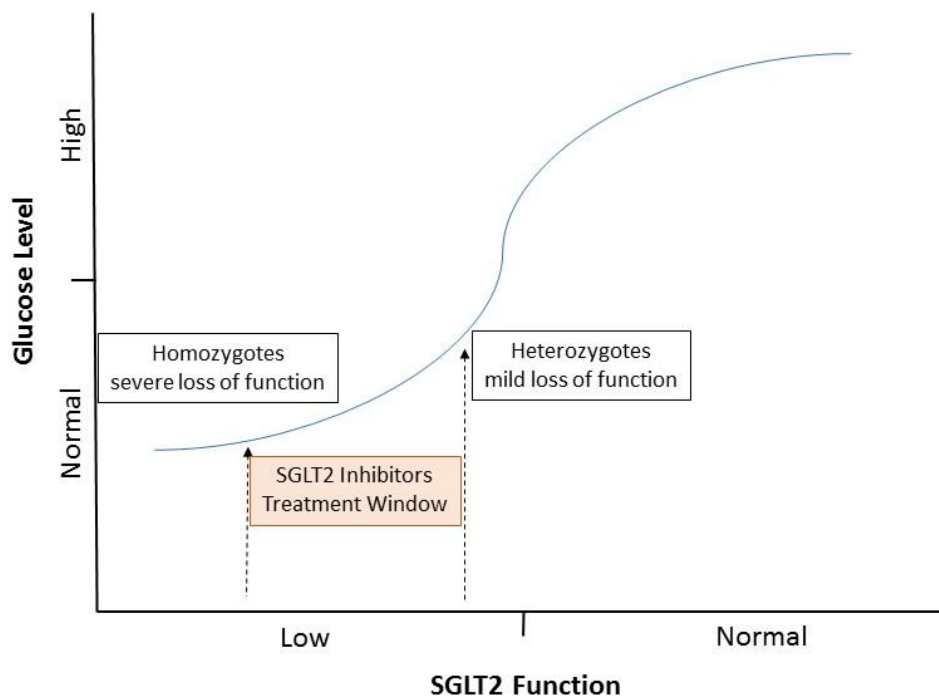
	Pharmacogenomics of antidiabetic drugs	Genomic studies of other diabetes mellitus-related traits
Sample sizes	Currently <10,000 individuals	Currently >100,000 individuals
Number of established variants	Only a few	>120 for T2DM risk >83 for other diabetes mellitus-related traits
Data type	Longitudinal	Cross sectional
Outcomes	Physiological response e.g. insulin secretion Treatment efficacy: glucose reduction Hard endpoints: cardiovascular risk Other outcomes: weight reduction	Onset of type 2 diabetes Hyperglycaemia: fasting glucose level, HbA1c levels Insulin resistance: HOMA-IR Insulin secretion: fasting insulin level, fasting C-peptide, HOMA-B

Table 1 | Pharmacogenomic studies of antidiabetic drugs and genomic studies of other diabetes mellitus-related traits

Table 1. This table highlights that the published GWAS of response to antidiabetic agents used considerably smaller sample sizes, and therefore established less variants, than those GWAS of other diabetes mellitus-related traits. Given that more longitudinal data in large samples are increasingly available through large bioresources such as the UkBiobank, pharmacogenomic studies are expected to provide more insights into the genetic basis of various drug response phenotypes.

Table 2. Replicated pharmacogenetic findings of antidiabetic agents

Agent	Treatment Efficacy	ADRs
Metformin	HbA1c reduction: *ATM*[39, 62]	Gastrointestinal side effects: OCT1[69, 73] Lactic Acidosis: (NA)
Sulfonylureas	HbA1c reduction: *TCF7L2*[52-54], *KCNJ11*[55-57] and *CYP2C9*[49, 51] Maintenance dose: *CYP2C9*[50]	Hypoglycaemia: *CYP2C9*[65]
Thiazolidinedione (TZDs)	HbA1c/Glucose reduction: *PPARG*[58-60]	troglitazone-induced hepatotoxicity: *GSTT1*[68] and *CYP2C19*[71]
Gliptins (DPP4i)	HbA1c reduction (insulin response): *CTRB1/2*[61]	pancreatitis and liver dysfunction: (NA)
SGLT2i	NA	genital and urinary tract infections: (NA)

NA means no evidence has been published on the drug-outcome pair.

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